Microcontainers for oral vaccine delivery

Nielsen, Line Hagner; von Halling Laier, Christoffer; Abid, Zarmeena; Keller, Stephan Sylvest; Boisen, Anja; Boyd, Ben; Rades, Thomas

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Microcontainers for oral vaccine delivery

Line Hagner Nielsen[1], Christoffer von Halling Laier[1], Zarmeena Abid[1], Stephan Sylvest Keller[1], Ben Boyd[2], Thomas Rades[3], Anja Boisen[1]

[1]The Danish National Research Foundation and Villum Foundation's Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Micro- and Nanotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark

[2]Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia;

[3]Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark

Aim

The purpose of these studies was to prepare glycerol monooleate (GMO)-based cubosomes carrying the model antigen ovalbumin (OVA) and the adjuvant Quil-A using spray drying as preparation method as well as to *in vitro* characterise these particles. Furthermore, the cubosome formulation was loaded into polymeric microdevices, called microcontainers (Fig. 1a), to be further tested for the potential application in oral vaccine delivery.

Methods

The cubosomes were prepared by dissolving the GMO, Dimodan® in ethanol (5.33 w/v%) and mixing it with an aqueous solution of dextran (stabiliser), OVA and Quil-A (2.63, 0.52, 0.035 mg/mL, respectively). After mixing, the solution was spray dried on a Büchi mini spray dryer. Cryo-TEM was used to verify the cubic particle morphology after reconstitution of the spray dried powder. Moreover, the size and zeta potential of the particles in aqueous suspension were measured by dynamic light scattering. The amount of loaded OVA and release of OVA from the cubosomes in PBS at pH 7.3 was measured by fluorescence. SU-8 microcontainers were fabricated using two steps of photolithography[1]. After *in vitro* characterisation, the cubosome powder was loaded into the microcontainers using a powder embossing method[2]. The microcontainers were manually filled with cubosomes and small-angle X-ray scattering (SAXS) was performed on the dry particles and when hydrated in buffer at pH 6.8. Furthermore, following vaccine-loading, a lid of the pH sensitive polymer Eudragit® L100-55 was deposited on the cavity of the microcontainers by a spray coating system for protection of the vaccine formulation through the stomach.

Results

SU-8 microcontainers had an inner diameter of 220 µm and a cavity depth of 270 µm (Fig. 1a). The spray drying process produced cubosomes as verified by cryo-TEM (Fig. 1b) and SAXS. The particle size of the cubosomes in suspension was 257±8 nm and the zeta potential was -18±0.6 mV. Approximately 106 µg of OVA was present in 1 mg of powder, and the release of OVA was fastest initially and gradually slowed down until 100 % was released within 24 h. Microcontainers was loaded with cubosomes and visualised using X-ray microtomography (Fig. 2). It was verified utilizing SAXS that the cubosomes was released from the microcontainers in buffer at pH 6.8, and the lid was deposited on the cubosomes-loaded microcontainers in a successful manner (Fig. 1C).

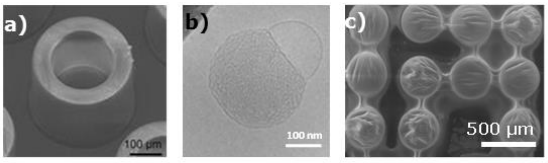

Fig. 1: a) SEM image of a microcontainer. b) cryo-TEM image of a cubosome. c) Eudragit-coatede cubosomes-loaded microcontainers

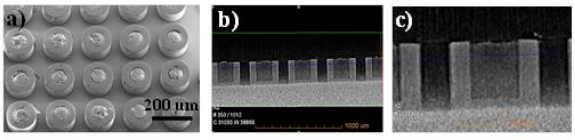

Fig. 2: Loading of the microcontainers with cubosomes. a): SEM image of the loaded microcontainers, and b) and c): x-ray microtomography images of the loaded microcontainers.

Conclusion

A dry powder of cubosomes loaded with OVA and Quil-A was produced by spray drying. After characterisation, the powder was loaded into microcontainers, and SAXS analyses indicated that cubosomes were released from the microcontainers.

References

[1] Nielsen LH et al. Int J Pharm (2016) 504 (1-2): 98-109. [2] Abid Z et al. Microelectronic Engineering (2017) 171: 20-24